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14. ABSTRACT

People differ in their susceptibility to abuse alcohol and drugs, and the factors that lead to abuse and dependence are not the same in everyone. Some people are susceptible because they experience particularly positive effects from alcohol and drugs. Often the same people have problems controlling their behavior. They are impulsive; they seek out novel and exciting experiences; and they may be influenced by other rewards, such as those associated with gambling or risky sexual behavior, even if the long-term consequences of those behaviors are harmful. In this study the relationship between the response to a stimulant drug and behavioral control was evaluated. First, 10-mg damphetamine was administered to healthy young men and women and groups of individuals with distinct stimulant responses to that drug were identified. Next event-related brain potentials (ERPs) were recorded while participants performed tasks that tap aspects of behavioral control: novelty detection, response inhibition, and reward processing. To evaluate the neural mechanisms involved in these processes, ERPs were recorded after placebo and 10-mg d-amphetamine (in separate sessions). The research identified neurocognitive measures of these processes that differ between responder groups. As such, the findings of this research may facilitate the development of targeted treatments for alcohol and drug abuse, as well as improved matching of treatments to individuals.

15. SUBJECT TERMS

event-related brain potentials (ERPs), stop P3, error-related negativities, P300, P3a, reorienting negativity (RON), response inhibition, reward processing, novelty detection, error-processing, vulnerability marker, cognitive control, amphetamine

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Amphetamine Challenge:
A Marker of Brain Function that Mediates Risk for Drug and Alcohol Abuse

W81XWH-07-2-0046 Cooperative Agreement

Principal Investigator: Frances H. Gabbay, Ph.D.

Final Report

August 5, 2011

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INTRODUCTION

More than one in six active duty military personnel report heavy use of alcohol, and binge-drinking rates are extremely high among the military as compared with civilians. As heavy alcohol use is considered one of the strongest predictors of alcohol abuse and dependence, many military personnel are at risk for these problems. In fact, 9.6% of all military personnel have experienced at least one alcohol-related serious consequence, 17.3% have had some loss of productivity related to alcohol use, and 12.3% meet some criteria for alcohol dependence. Thus, effective evidence-based intervention and preventive strategies will improve the health and well-being of military personnel as well as military readiness.

People differ widely in their susceptibility to abuse alcohol and other drugs, and the factors that lead to abuse and dependence may not be the same in all people. Some people are susceptible because they experience particularly positive effects from alcohol and drugs—the drugs make them feel good. Often, the same people have problems controlling their behavior. They are impulsive—it may be difficult for them to stop a behavior, even if they realize it could lead to a bad outcome. They seek out novel and exciting experiences, often without considering the consequences, and may be strongly influenced by other rewards. They do things that may lead to short-term rewards, such as gambling or risky sexual behavior, even if the long-term consequences may be harmful. When these tendencies occur together, individuals are more likely to try alcohol or drugs at a young age and to use them more frequently and in larger quantities, and are more likely to continue using these substances and develop problems related to their use.

We do not know why some people experience a heightened positive—or stimulant—effect of alcohol and drugs, or why this characteristic is sometimes associated with poor control. One possibility is that the same neural system—namely, the mesolimbic dopamine system—mediates the response to stimulant drugs as well as aspects of behavioral control. This system may affect risk for frequent and heavy alcohol and drug use through its effects on the stimulant response, as well as those on other putative risk factors, including novelty-seeking, reward sensitivity, and impulsivity. As variability in the function of this system may be proximally indicated by individual differences in the amphetamine response, an amphetamine challenge provides a rough metric of neural function that is associated with risk in various ways.

Accordingly, in the first phase of this study, we administered to young men and women 10 mg *d*-amphetamine, a drug with stimulant effects similar to those of alcohol and other drugs. We then selected groups of individuals who experienced distinct stimulant responses to the drug. Next, in two separate sessions, we recorded event-related brain potentials (ERPs) while these individuals performed three tasks designed to tap aspects of behavioral control: (a) a *novelty oddball task* to assess the brain's response to novelty; (b) a *stop-signal task* to assess neurocognitive processes associated with response inhibition; and (c) a *gambling task* to assess the brain's response to wins and losses. In one of the two sessions, we administered a placebo; in a separate session, we administered 10 mg *d*-amphetamine.

The results of this study will help us to understand the association between the stimulant response and aspects of behavioral control. As such, the results may lead to better treatments, particularly for people who abuse alcohol and other drugs because of their stimulating effects, and who seek novel and immediately rewarding experiences or make impulsive decisions. As such, the findings may have immediate and long-term implications for the health and well-being of military personnel.

PROBLEMS

As described in our quarterly and annual project reports, the project was delayed several times for substantial periods of time, for reasons beyond our control. First, as a result of the Walter Reed Army Medical Center–National Naval Medical Center (NNMC) Base Realignment and Closure effort, our lab was relocated from the main USU campus to a USU annex, a separate building on the grounds of the NNMC. The new space was not configured to accommodate electrophysiological recording and other demands of the research protocol; thus, the space required substantial renovation. Planning and overseeing the renovations, as well as dismantling and rebuilding the lab, required substantial time and focus. The move occurred as we were piloting cognitive tasks to be used in the research. This pilot work had to be suspended during the move and subsequent renovations. Moreover, after the move was completed, it was necessary to restart the pilot work, to ensure that we were obtaining valid recordings in the new lab. Whereas the new space accommodated the project more effectively than did the old, significant time was lost during this process.

We used this forced hiatus in testing to improve the protocol in a number of ways that allowed us to address our specific aims more efficiently and completely. However, these improvements in the protocol needed to be approved by the USU Institutional Review Board (IRB). Thus, although the project initially received approval by the USU IRB on 12/4/06 (i.e., after notification of the award but before the award began), the amendments did not receive final approval by the USU IRB until 5/23/08. The revised protocol received approval from the U.S. Army Medical Research and Materiel Command Office of Research Protections on 7/3/08. Thus, this process took considerably longer than the six months we allotted in the Statement of Work.

More recently, the screening of potential participants was disrupted when our nurse practitioner (NP) resigned unexpectedly. Because all participants must be carefully screened, including a physical exam by an NP, this issue imposed a delay on data collection. We identified a replacement NP and submitted a collaborative agreement application for the NP to the Maryland Board of Nursing (as is required for NPs practicing in Maryland). While we awaited approval of the agreement, the NP found a higher-paying position and left the project, leaving us to start the process all over again. Once more, we identified a new NP and submitted the collaborative agreement for her; however, due to a problem at the Board, approval of that agreement was took a full month longer than it should have.

During the four months it took to resolve this problem, we were able to continue screening (and thus testing) as a result of assistance we received from an NP on the faculty of the USU School of Nursing. He conducted exams as his schedule permitted, which allowed us to proceed, albeit at a much slower pace than our timetable demands. During this time, we processed data and developed more automated ways of accomplishing this task. These automated data processing procedures later allowed us to process and analyze our data more efficiently.

In sum, we resolved all problems and consistently used ―down time" to improve the protocol in important ways. Nonetheless, due to the substantial delays in data collection that occurred while these issues were being resolved, we were not able to complete the tasks listed in the Statement of Work within the original project period. Thus, we requested (and were granted) a no-cost extension to complete data collection, processing, and analysis. The balance of this report describes our accomplishments in terms of (a) number of participants tested, (b) tasks listed on the Statement of Work, (c) research findings, and (d) presentations and publications.

PROGRESS

Number of Participants Tested

As one measure of our accomplishments, Table 1 presents the number of participants tested in each phase of the study. The purpose of the web survey was to identify individuals who did not meet preliminary inclusion criteria (and thereby to save resources by excluding these individuals before on-site screening). In the health-screening session, which included a physical exam by a nurse practitioner, we determined whether individuals met the criteria for inclusion in the protocol. These criteria were designed to (a) minimize risk to participants and (b) maximize our ability to detect responder-group differences by reducing heterogeneity. The purpose of the medication-response session was to identify individuals exhibiting distinct stimulant responses to *d*-amphetamine. Finally, in the ERP sessions, we evaluated in these individuals neurocognitive processes associated with the response to novelty and reward and with response inhibition—after placebo and, in a separate session, after 10-mg *d*-amphetamine. The analogous numbers we reported in our last annual report (6/25/10) are also provided.

Table 1. Participants completing each phase of the protocol

Phase of Study	June 2010	June 2011
Respondents to recruitment notices	5,935	9,822
Web survey (1 h)	1,503	1,970
Health screening (3 h)	596	599
Medication-response session (4.5 h)	170	217
Two ERP sessions (4.5 h x 2)	92	113

Statement of Work

In this section, we state progress made in terms of the tasks listed in our *Statement of Work,* as we have done in each of our quarterly reports.

Task 1: Developed and submitted protocol and supporting materials to local (USU) Institutional Review Board (IRB); revised the protocol to meet IRB stipulations; and provided IRB approval letter to USAMRAA.

Task 2: Submitted protocol and supporting materials to USAMRMC Human Subjects Research Review Board (HSRRB); and on 7/03/08, obtained approval for the protocol as well as for amendments to improve the original protocol.

Task 3: Modified software to run the three cognitive tasks as specified for the study: (a) novelty oddball, (b) stop-signal, and (c) gambling.

Task 4: Recruited, hired and trained study personnel to execute all procedures for the study and ordered supplies for the study.

Task 5: Placed advertisements and distributed flyers about the study and fielded responses to those notices.

Task 6: Recruited candidates to complete web survey, in order to identify the first 48% of the sample; reviewed survey results; identified eligible candidates; and scheduled health-screening appointments.

Task 7: Conducted a 3-h health-screening session for each candidate; reviewed results of those screening sessions; and organized physical examinations for eligible candidates.

Task 8: Conducted a physical examination of each eligible candidate; reviewed results of those exams to determine eligibility for the study; and scheduled each eligible candidate for a medication-response session.

Task 9: Conducted a 4.5-h medication-response session for each participant, ensuring that women were tested between Day 2 and Day 9 of their menstrual cycle; scored Biphasic Alcohol Effects Scale completed by each participant, to identify those with distinct stimulant responses; and scheduled participants for ERP sessions.

Task 10: Tested each participant in two 4.5-h ERP sessions, ensuring that a minimum of 48 h intervened between the two sessions for each participant and that women were tested between Day 2 and Day 9 of their menstrual cycle.

Task 11: Backed up ERP data from each testing session; executed blink-correction algorithm; averaged, quantified, and plotted ERP data for each participant; and reviewed plots and the quantified data for each participant.

Task 12: Conducted preliminary analysis of ERP data and presented results at annual meetings of the *Society for Psychophysiological Research*, *Research Society on Alcoholism*, and *College of Problems in Drug Dependence*, and at the *Third Military Health Research Forum*.

Task 13: Scored and analyzed subjective effects inventories collected during ERP sessions.

Task 14: Recruited additional candidates to complete web survey, in order to identify the last 52% of the sample; reviewed survey results; identified eligible candidates; and scheduled health-screening appointments.

Task 15: Conducted a 3-h health-screening session for each candidate; reviewed results of those screening sessions; and organized physical examinations for eligible candidates.

Task 16: Conducted a physical examination of each eligible candidate; reviewed results of those exams to determine eligibility for the study; and scheduled each eligible candidate for a medication-response session.

Task 17: Conducted a 4.5-h medication-response session for each participant, ensuring that women were tested between Day 2 and Day 9 of their menstrual cycle; scored Biphasic Alcohol Effects Scale completed by each participant, to identify those with distinct stimulant responses; and scheduled participants for ERP sessions.

Task 18: Tested each participant in two 4.5-h ERP sessions, ensuring that a minimum of 48 h intervened between the two sessions for each participant and that women were tested between Day 2 and Day 9 of their menstrual cycle.

Task 19: Backed up ERP data from each testing session; executed blink-correction algorithm; averaged, quantified, and plotted ERP data for each participant; and reviewed plots and the quantified data for each participant.

Task 20: Adapted laboratory software in preparation for comprehensive analysis of ERP data.

Task 21: Tested remaining participants in two 4.5-h ERP sessions, ensuring that a minimum of 48 h intervened between the two sessions for each participant and that women were tested between Day 2 and Day 9 of their menstrual cycle.

Task 22: Backed up ERP data from the last testing sessions; executed blink-correction algorithm; averaged, quantified, and plotted ERP data for each participant; and reviewed plots and the quantified data for each participant.

Task 23: For each task in the ERP battery, prepared grand-mean ERPs for each of the groups; and for each task, conducted statistical analysis of ERP data.

Task 24: Prepared manuscripts for submission to peer-reviewed scientific journals; submitted manuscripts; and prepared outlines of additional manuscripts.

Task 25: Outlined the immediate and long-term implications of the findings for the health and well-being of military personnel, in preparation for an additional paper aimed at military commanders and health-care providers.

Task 26: Prepared report for USAMRAA.

KEY RESEARCH ACCOMPLISHMENTS

Overview

Considerable evidence suggests that the stimulant response is a marker of risk for alcohol and drug abuse. Whereas this likely reflects in part the rewarding effects of these substances, it may also be the result of other putative risk factors that have been associated with the stimulant response—namely novelty- and reward-seeking and impulsivity. In this context, we present evidence obtained in the present study of striking individual differences in the magnitude of the stimulant response, which we used to define groups with distinct stimulant responses to amphetamine. We then present a brief summary of our finding of associations between the stimulant response and measures of alcohol and drug use, which reinforce the idea that the subjective stimulant response is a marker of risk. Next we discuss our findings of neurocognitive differences between responder groups, which were identified using event-related brain potentials recorded during the performance of three cognitive tasks. These differences are consistent with the view that an enhanced stimulant response may affect risk for alcohol and substance use disorders directly via its effects on the subjective component of reward or indirectly, as a result of its association with the response to novelty, reward salience, and inhibitory control.

Individual Differences in the Stimulant Response

In an initial session we administered to young men and women 10 mg *d*-amphetamine, a drug with stimulant effects similar to those of alcohol and other drugs. Substantial evidence implicates the mesocorticolimbic dopamine pathway as a mediator of the stimulant effects of amphetamine. In this session, three groups of individuals exhibiting distinct responses to 10-mg *d*-amphetamine were identified: *Responders* reported strong, positive feelings; *Nonresponders* did not; and *Average Responders* fell between these two groups (see Figure 1). By definition, the ratings of Responders were greater after *d*-amphetamine than at baseline, whereas there was little change in *Stimulated* scores for Nonresponders after the drug as compared to baseline.
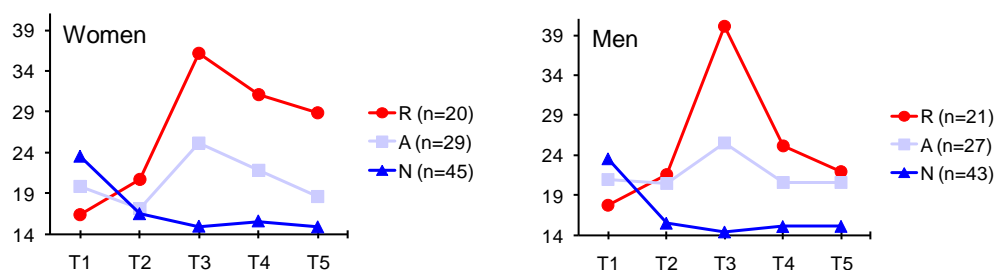

Figure 1. Mean scores on the Biphasic Alcohol Effects Scale (BAES) for women (left) and men (right) in three responder groups. The BAES was administered before (T1) and four times after 10-mg *d*-amphetamine, to identify groups of individuals with distinct subjective stimulant responses. Group membership was determined in an initial session, with at least two days intervening before the first ERP session. *Note*. R = Responder; A = Average Responder; N = Nonresponder

Stimulant Response and Substance Use

Consistent with previous research, the results of the present study suggested that an enhanced stimulant response, assessed with an amphetamine challenge, may be a marker of risk for alcohol and drug use. Notably, a heightened stimulant response predicted aspects of alcohol and drug use that have been empirically associated with novelty-seeking, reward valuation, and impulsivity: age of onset of regular alcohol use, frequency of marijuana use, and ever having used alcohol, marijuana, or any other illicit drug. The study also provided evidence of some gender-specific effects—for women, the stimulant response also predicted average daily alcohol consumption and frequency of intoxication.

Moreover, an unexpected finding was that the combination of an enhanced stimulant response and high negative emotionality (measured with the Multidimensional Personality Questionnaire) predicted multiple indices of heavy and problematic alcohol use in both women and men, and in women the combination of the two risk factors also predicted frequency of marijuana use. That is, among individuals high in negative emotionality, an enhanced stimulant response was particularly strongly related to risky alcohol use.

It is possible that negative emotionality may motivate behaviors to reduce negative affect; when it co-occurs with traits known to be associated with an enhanced stimulant response, including reward- and novelty-seeking and impulsivity, there may be a bias in favor of seeking novel or immediately rewarding outcomes, or engaging in impulsive behaviors to cope with (or distract from) negative affect. In contrast, individuals high in negative emotionality but lacking a strong stimulant response—and therefore, we hypothesize, with low levels of this constellation of traits—may engage in other forms of emotion regulation. This may have important implications for understanding alcohol and drug abuse that co-occurs with post-traumatic stress disorder, for which negative emotionality is an important risk factor.

In summary, we found that the amphetamine response was associated with measures of risky alcohol and substance use. In the case of some of these measures, an enhanced amphetamine response alone predicted risky substance use; in other cases, the combination of an enhanced amphetamine response and a high level of negative affect was a stronger predictor. These associations likely reflect in part the effects of reward—individuals who experience more positive effects are more likely to use alcohol and other drugs more often and in larger quantities. In addition, however, the associations may reflect the effects of the demonstrated covariance between amphetamine response and other putative risk factors—namely, reward- and novelty seeking and impulsivity—that have been empirically associated with stimulant response.

Neurocognitive Metrics of Risk

As predicted, and in keeping with the view that shared mediation by a common neural mechanism accounts for a cluster of risk traits that includes the stimulant response, neurocognitive differences between Responders and Nonresponders were evident in all three of the cognitive tasks in the test battery.

Novelty oddball task. Involuntary attention shifting is a fundamental cognitive operation. Whereas this automatic shift in focus is adaptive in that it allows an individual to orient to unexpected and potentially harmful changes in the environment, attentional shifts need to be

controlled during goal-directed behavior. Research using the *novelty oddball task* has identified an ERP component, P3a, which reflects the involuntary shift in attention to a deviant, or novel, stimulus. In this task, a series of stimuli comprising two categories is presented. One of the categories of stimuli—the oddball—occurs infrequently. The participant is instructed to make one response to the oddball stimulus (also called the target), and to make another response (or no response) to the frequent stimulus (the standard). During the series, a third class of stimuli is presented. In contrast to standards and targets, these rare nontargets are irrelevant to the task. P3a is considered the electrical brain correlate of the orienting response. This component occurs approximately 300 ms after a deviant stimulus and is largest at frontal electrode sites. Prefrontal cortex is critical in novelty processing; in particular, recent evidence suggests that P3a can be sourced to the anterior cingulate cortex. Important to the rationale for the present study, the mesolimbic dopamine system is implicated in the response to novelty.
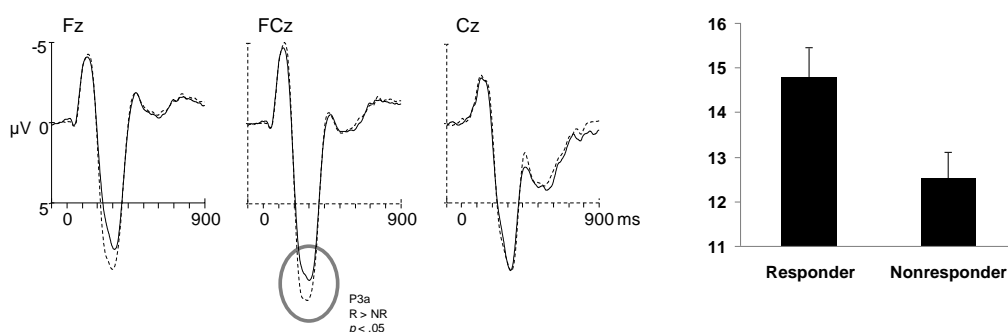

Figure 2. (a) On the left, ERPs elicited by novel sounds ($p = .10$; displayed at Fz, FCz, and Cz) in the novelty oddball task. Grand averages, collapsed across placebo and 10-mg *d*-amphetamine conditions, are superimposed for Responders (dashed line) and Nonresponders (solid line). In the right panel, P3a amplitude (in µV) is presented for Responders and Nonresponders. P3a was larger in Responders than Nonresponders ($p < .05$).

Our findings suggest that Responders are more vulnerable to the effects of novelty: P3a was larger in Responders than in Nonresponders, after placebo as well as *d*-amphetamine (see Figures 2a and 2b). That is, the attention shift to task-irrelevant novel stimuli was greater in Responders than in Nonresponders, which suggests that novelty is more salient—and possibly more rewarding—for Responders. That the difference was evident after placebo as well as amphetamine suggests further that the more pronounced shift in attention to novel sounds by Responders reflects a trait-like difference in brain function. This finding is consistent with the idea that there is overlap between neural structures supporting stimulant and novelty response. It is possible that the phasic release in dopamine in response to amphetamine as well as that to novelty is enhanced in Responders.

We also found that, in Responders, P300 amplitude was larger after amphetamine than after placebo; whereas, in contrast, there was a small and non-significant increase in P300 amplitude in Nonresponders after amphetamine as compared to placebo (see Figures 3a and 3b, next page). This suggests that in Responders but not Nonresponders, amphetamine facilitated the allocation of resources to processing targets. That is, in individuals who reported feeling energized after amphetamine, the drug enhanced the allocation of attention to the target stimuli in a discrimination task. This suggests that P300 reflects a process integral to subjective energizing effect of amphetamine.
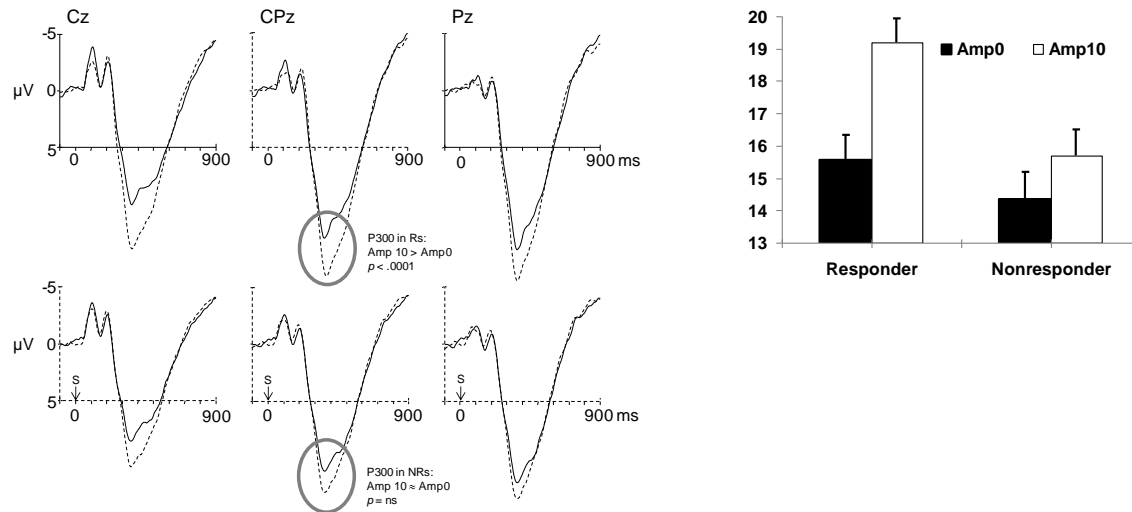
Figure 3. On the left, ERPs elicited by rare target tones (*p* = .10; displayed at Cz, CPz, and Pz) in the novelty oddball task. Grand averages representing ERPs recorded after placebo (solid lines) and 10-mg *d*-amphetamine (dashed lines) are superimposed, separately for *Responders* (top row) and *Nonresponders* (bottom row). In the right panel, P300 amplitude (in µV) is presented for the placebo (black bars) and amphetamine (open bars) conditions, separately for Responders and Nonresponders. In Responders, P300 recorded after amphetamine was larger than that recorded after placebo (*p* < .0001), whereas in Nonresponders, amphetamine did not significantly increase the amplitude of P300 (*p* = ns).

In sum, the results we obtained for the novelty oddball task suggest that an enhanced subjective stimulant response is associated with (a) enhanced neurocognitive response to novelty and (b) an enhanced effect of amphetamine on effortful attention. As the responses to novelty and to amphetamine are thought to depend in part on dopamine function, the responder-group differences may reflect variability in that system. Phasic dopamine release in response to amphetamine or novelty may be blunted or enhanced, depending on baseline dopamine function. Subjective response to an amphetamine challenge may serve as a proximal metric of this variability in function.

Stop-signal task. The ability to evaluate and adjust behavior by means of inhibitory intervention is crucial for the maintenance and control of cognitive and motor events. Stopping an ongoing motor response is a key element of that control. Response inhibition is considered the result of a balance between activating and inhibitory processes. Stop-signal tasks based on this ―horse-race" model provide laboratory measures of the ability to inhibit primed behavioral responses. In one version of this task, two reaction (or *go*) stimuli are presented in random order and equally frequently. Participants are instructed to press a button as quickly as possible with their left or right index finger to the *go* stimuli. In a subset of trials, however, the *go* stimulus is followed by a *stop* signal, presented at variable delays. Participants are instructed to abort their response on these *stop* trials. Thus, these tasks require choice responses to *go* signals and inhibition of responses to unpredictable *stop* signals.

ERPs recorded during a stop-signal task provide representations of the activating (*go*) and inhibiting (*stop*) processes in the brain. The stop signal elicits a set of ERP components including Stop P3, which reflects processes involved in successful and unsuccessful inhibiting of a response following a *stop* signal. Recent evidence implicates inferior frontal and mid-cingulate cortex in these ERP components. In the present study, among women, after placebo, Stop P3 was

larger in Responders than Nonresponders; moreover, the difference was larger after amphetamine. This suggests that female Responders allocated more inhibitory resources to the task as compared to female Nonresponders, suggesting that they had greater difficulty withholding a prepotent response.

Whereas no group difference in Stop P3 was evident among men, the stop task revealed behavioral differences between male Responders and Nonresponders. For mean reaction time (RT) to *Go* stimuli, considered a measure of activation, there was a significant Dose × Responder Group × Gender interaction ($p = .0272$) (see Figures 4a and 4b). Follow-up analyses revealed a Dose × Responder Group effect in men ($p = .0461$) but not women: There was a trend for amphetamine to have an activating effect in male Responders ($p = .0737$) whereas the apparent (and paradoxical) increase in RT after amphetamine in male Nonresponders was not significant.
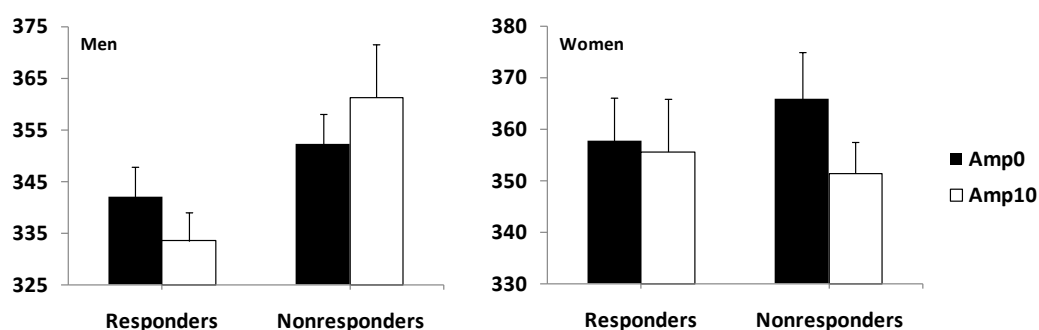

Figure 4. Mean reaction time to *Go* stimuli in the stop-signal task are presented for men (left panel) and women (right panel), after placebo (black bars) and amphetamine (open bars). In each panel, the results are displayed separately for *Responders* and *Nonresponders*.

Gambling task. It is essential for survival for an organism to determine the affective or motivational significance of ongoing events, and it is likely that mechanisms have evolved to permit rapid evaluations of the reward value of stimuli encountered in the environment. Individual differences in this evaluation process may affect behavioral control—over- or under-valuation of rewards may be associated with risky behavioral choices. Several gambling tasks have been developed that permit the study of reward processing in the laboratory. In one such task, participants are required to select between two colored cards that are unpredictably associated with small and large monetary gains and losses. After they make a choice, participants learn whether they won or lost a large or small amount of money. Next, they learn what they would have won or lost if they had chosen the other card. P300 elicited by feedback in a gambling task is thought to reflect the affective significance of that feedback.

As expected, P300 elicited by wins was larger than that elicited by losses, in women and men. In addition, however, in women, P300 elicited by wins and losses was larger in Nonresponders than in Responders; whereas in men, no group difference in P300 was evident (see Figure 5). This suggests that among women, Nonresponders judge feedback about wins and losses to be of greater affective significance as compared to Responders. This finding was counter to our prediction: It was expected that individuals with an enhanced stimulant response (i.e., Responders) would over-value monetary reward as reflected in a larger P300 elicited by

feedback in the gambling task. That there was a group difference suggests that there is indeed overlap in the neural mediators of amphetamine response and reward valuation but that the nature of that relationship is more complex than originally predicted.
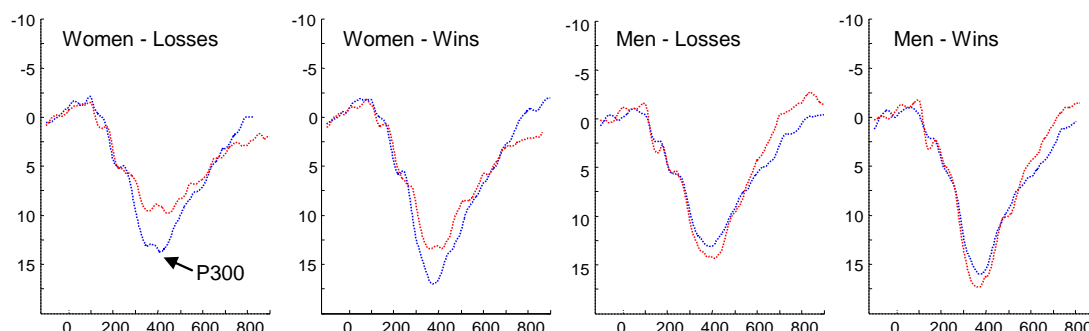

Figure 5. ERPs elicited after placebo by wins and losses in a gambling task. Grand-average ERPs (at FCz) are superimposed for Responders (solid red) and Nonresponders (dashed blue). Grand averages are presented separately for women and men. P300 elicited by feedback in a gambling task is thought to reflect the affective significance of that feedback. As expected, P300 elicited by wins was larger than that elicited by losses, in women and men. In women, P300 was larger in Nonresponders than in Responders, suggesting that Nonresponders considered both wins and losses to be more significant than Responders did. In men, no group difference in P300 was evident.

Summary. Taken together, the responder-group differences observed in the novelty oddball, stop-signal, and gambling tasks in the present study are consistent with behavioral and clinical data that suggest phenotypic covariance between the stimulant response, that to novelty and reward, and impulsivity. This variability may reflect overlap in the neural systems—some of which may be gender-specific—that support the subjective stimulant response and those that support the novelty, reward valuation, and aspects of inhibitory processing.

Implications

Despite tremendous progress over the past two decades in the development and validation of behavioral and pharmacological treatments for drug abuse and dependence, critical challenges remain. Even the most efficacious treatments are not universally effective, and individuals who benefit from those treatments do not improve quickly or completely.

Current approaches to medication development rely heavily on empirical data implicating the dopamine system in drug abuse and dependence. These approaches include medications that inhibit the dopamine spike triggered by drugs of abuse; those that activate the same neurotransmitter system as an abused drug but produce no dopamine spike; and others that slightly increase the amount of dopamine that cells release when a person engages in normally rewarding activities, with the aim of enabling addicted individuals to once again feel pleasure.

To the extent that individuals are characterized by differently functioning dopamine systems, these therapies may be more or less effective and may be associated with more or fewer side effects. Similarly, such differences may mitigate the efficacy of behavioral therapies. Accordingly, the findings from the present study may improve our ability to improve and evaluate therapies and facilitate efforts to match therapies to individuals.

REPORTABLE OUTCOMES

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